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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/005,073 | JEVNIKAR ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *52-101* is/are pending in the application.

4a) Of the above claim(s) *53-58,62,64-68,92-94 and 96-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,59-61,63,69-91 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Claims 53-58, 62, 64-68, 92-94, and 96-101 stand withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected species.

Claims 52, 59-61, 63, 69-91, and 95 are being acted upon.

2. Applicant's Remarks and Terminal Disclaimer filed 10/09/07 are acknowledged. The Terminal Disclaimer has obviated the previous rejection for obviousness-type double patenting in view of U.S. Patent No. 6,338,850.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 52, 59-61, 63, 69-91, and 95 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature

of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts were such that no methods were available in 1994 for inducing oral tolerance to a transplantation antigen in a human. Indeed, some 10 years later, with the possible exception of some allergy and Rh antigens, therapeutic tolerance has not been demonstrated to be inducible in humans.

Note that the claims comprise both product and method claims. Also note that only Claims 77 and 83 recite the limitation that the method and products are intended for use in humans. It is clear however, that the products of the claims are intended for just one use, i.e., the induction of oral tolerance to transplantation antigens. It is also well-known that transplantation is performed almost exclusively in humans. Accordingly, all of the claims under examination are rejected for lack of enablement.

Attempts to induce tolerance in humans have been completely unsuccessful in at least two different documented instances. See for example, *Marketletter* (9/13/99) which teaches the complete failure of tolerance induction in human trials. Both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) provided successful results in inducing tolerance in animal models, however, both were complete failures in human trials. Also note an additional more recent reference (Goodnow, 2001), wherein the author flatly states, "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles," (see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2). WO 02/053092 teaches that the oral administration of antigens for the induction of tolerance presents numerous additional "obstacles" including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that "oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation," (page 23). Clearly then, the brief teachings of the instant disclosure, wherein no *in vivo* nor even *in vitro* data is disclosed, cannot be considered to be enabling for the method and products of the instant claims.

*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data relevant to the induction of tolerance, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

As set forth in the action of 4/08/05, Applicant's arguments, filed 2/08/05, have been fully considered but they are not persuasive. Applicant's remarks highlight the points and arguments of the instant declaration of Inventor Jevnikar. Accordingly, the declaration is addressed here.

The Inventor begins by discounting the teachings of the 1999 Marketletter Newsletter because the newspaper publication is not peer reviewed and may contain errors.

It is noted that Applicant has not actually addressed the substance of the document, i.e., that compositions that were successful in inducing tolerance in animal models were not successful in humans. This teaching alone clearly establishes the unpredictability of the claimed methods and compositions.

The Inventor argues that the reference to unpredictability in the Goodnow (2001) paper refers to the use and mechanism of action of corticosteroids.

Applicant is simply incorrect, or at best incomplete, in his description of the Goodnow reference. The unpredictability also refers to methods of "chronically stimulating antigen receptors with antigen or antibodies to the receptor", i.e., methods of inducing tolerance.

The Inventor argues that the teachings of WO 02/053092 do not involve oral administration of plant materials, but the reference does show that immune tolerance can be accomplished.

It is the Examiner's position that the reference teaches what it teaches - the induction of oral tolerance is fraught with numerous obstacles not addressed in the instant application. Also note that the Inventor has not addressed the teaching of the reference that the induction of oral tolerance requires "extensive empirical experimentation". Additionally, it must be noted that even though the Inventor discounted the factual teachings of the Marketletter document (i.e., that oral tolerance trials were stopped) because it was not peer reviewed, the Inventor here accepts certain teachings that might support the inventions of the instant claims, even though the teachings of a WO document also are not peer reviewed.

The Inventor states, "I further disagree with the Examiner's statement that oral tolerance has never before been successfully demonstrated in humans".

What the Examiner actually wrote in the previous action was:
"Whereas tolerance has been repeatedly induced in mice, the identical/equivalent methods have not worked in humans".

The Inventor has submitted two references, Husby et al. (1994) and McKown et al. (2000), assertedly teaching the induction of tolerance in humans.

Regarding the Husby et al. reference, the reference teaches the reduction of *in vitro* T cell proliferation and delayed skin test responses to KLH. The reference further teaches that no reduction in B cell responses was observed. The authors speculate that it was only a Th1 response that was reduced. Clearly then, the reference cannot enable the broad methods and compositions of the instant claims that recite the suppressing or reducing of *any* type of immune response. Interestingly, the authors point to the clinical studies of Weiner et al. to address the question of whether or not the feeding of antigens can be used to treat MS or RA. It is those very studies that were reported as being stopped in the *Marketletter* reference.

Upon further review of the work of the scientific group of which Husby was a member, Elson et al., it was found that the group reported in 2004 (Moldoveanu et al.) the failure of oral tolerance in suppressing an ongoing immune response. Using the same KLH antigen model as used some ten years earlier in Husby et al., the reference states "some form of immunomodulation greater than that provided by

the oral administration of antigen alone is required in humans for suppression of an existing immune response". This would appear to be a direct teaching that the inventions of the instant claims cannot work as broadly claimed.

Regarding the McKown et al reference., the reference provides encouraging preliminary data indicating that oral administration of type I collagen (CI) might be useful for treating systemic sclerosis (SSc). Note that regarding tolerance, however, the reference teaches only that IFNγ production was reduced which, "suggests that oral tolerance to CI was effected". Note another teaching of the reference, specifically, an unexplainable reduction in IL-10 (which was previously reported to be *upregulated* in other models of oral tolerance). Also note the conclusions of the reference, i.e., "Further evaluation of oral tolerance to CI in patients with SSc is justified," and "Oral CI administration appears to be safe. Its efficacy needs to be assessed by a larger placebo-controlled, double-blind trial". It appears then that even this specific embodiment of the induction of oral tolerance has not risen past the level of idea. Thus, it cannot support the broad inventions of the instant claims.

Upon further review the work of the scientific group including McKown et al., numerous examples in which no sign of oral tolerance induction could be induced can be found. See for example, McKown et al. (1999), in which the authors document the lack of efficacy of the oral administration of type II collagen for the treatment of RA. More interestingly, see Carbone et al. (2004) in which, in this instance, the oral administration of CI had no effect on SSc patients. Given the same group's report of encouraging results with the same composition in the same patients four years earlier in the McKown et al. (2000) reference, it would appear that the group was simply employing methods of trial-and-error (unsuccessfully) in their attempts to induce tolerance in SSc patients. As methods of trial-and-error provide no particular expectation of success with any particular embodiment (as aptly demonstrated here), said methods are considered to be inherently unpredictable and requiring of undue experimentation. Further note that this *demonstration* of unpredictability in 2004 must call into question the enablement of the methods and compositions of the instant claims that claim priority to 1993.

The Inventor asserts that the unpublished results of an NIH trial demonstrate that oral tolerance can be induced in humans.

The Examiner cannot evaluate or comment on data that has not been submitted for review.

The Inventor argues that the use of the term "unexpected" in a previous declaration was not an admission of the unexpected nature of the instant invention.

It is presumed that the previous declaration was prepared and reviewed with the assistance of representatives skilled in patent prosecution, i.e., Applicant is not *pro se*. Accordingly, Applicant's choice of the terms "not predictable" in section 12 and "unexpected" in section 14 must be considered to be intentional and the terms must be considered to have their normal meanings when used in the patent prosecution context.

The Inventor asserts, "In the case of both mice and humans, immune responses in lymphocytes upon *in vitro* challenge to a specific protein is similarly attenuated or changed following oral administration of the protein. No qualitative or quantitative differences are found in the pattern of cytokines

released or T cell activity and so mice and humans share a common biological response to oral protein antigens".

The Inventor's unsupported assertions aside, the facts of record clearly demonstrate that the induction of tolerance in humans is at best highly unpredictable. Even in the few documented instances wherein some degree of T cell tolerance may have been established, e.g., Husby et al. (1994), said possible tolerance appears to have been the result of random chance or simple trial-and-error, given the documented failures of the same groups, e.g., Moldoveanu et al. (2004). The Examiner cannot simply ignore the failure upon failure in establishing efficacious tolerance in humans set forth in the prior art. And it must be noted that the methods and compositions of the instant claims recite essentially *no* limitations as regard the diseases to be treated or the antigens to be used. Further note that the specification provides *no* guidance regarding the parameters of tolerance induction, e.g., dosages to be used or the timing of administration. Finally, assuming *arguendo*, that tolerance in humans has been demonstrated, e.g., the unpublished NIH study set forth in the Inventor's declaration, it is unclear how results still unpublished in 2005 could enable the instant claims as of their priority date of 1993.

As set forth in the action of 1/11/06, Applicant's arguments, filed 10/18/05, have been fully considered but they are not persuasive. Applicant attempts to discount the teachings of the *Marketletter* as did the Inventor previously, e.g., it lacks credibility and is not peer reviewed. Applicant argues that the teachings are "anecdotal" and do not report a definitive scientific conclusion.

It is unclear to the Examiner how peer review would alter the teachings of the report that trials were stopped because they were failures? It is further unclear to the Examiner what Applicant's characterizing the teachings of the report as "anecdotal" is intended to mean. Is Applicant arguing that the trials were not actually stopped? Even Applicant admits that the trials reported in the *Marketletter* were stopped because "the statistical significance of the results did not warrant further spending on late clinical trials" which would seem to be scientific conclusion, i.e., the drug did not work. Also note that the report states that the drug first failed in phase II trials but was pushed into phase III trials regardless where it again failed to show "statistically significant results".

Applicant asserts that the Examiner is in error with respect to the Goodnow reference and that "the unpredictability described by Goodnow refers to the use and mechanism of action of corticosteroids". Applicant argues that the reference does not say that oral tolerance does not work and further argues that the reference states that clinical trials are underway. Applicant then dismisses the reference as mere opinion.

The reference states in the *Abstract*, "New experimental therapies aim to mimic tolerogenic antigen signals by chronically stimulating antigen receptors with antigens or antibodies to the receptor, or aim to block costimulatory pathways involving CD40 ligand, B7, or interleukin 2. Obtaining the desired response with these strategies is unpredictable because many of these signals have both tolerogenic and immunogenic roles." This "unpredictability does not appear to be referring to the "mechanism of action of corticosteroids" as Applicant asserts. Regarding the teaching that trials are underway, said teaching is noted. Also note, however, that the report does not indicate whether said trials are merely safety trials (phase I) or efficacy trials (phase II or III), thus nothing

can be deduced from this teaching. And as set forth previously, the instant record contains no reports of success in oral tolerance trials, but it does contain reports of multiple failures in oral tolerance trials. Additionally, a complete reading of the reference would include a review of the teachings of the second column of page 2120 wherein the author further states that while mucosal tolerance has been achieved in experimental animals, "The first clinical trial of oral tolerance was unsuccessful, pointing to the need to understand better the mechanisms involved and to develop ways to achieve more reliable linkage between tolerogenic antigen suitable tolerogenic costimuli". It is noted that no such attempt is made in the instant application. Finally note that while Applicant dismisses the opinion of the author, the American Association of Immunologists has recently named him a keynote speaker for the 2006 meeting of the AAI; the November/December 2005 AAI Newsletter states that Dr. Goodnow's work "has changed the conceptual framework of self-tolerance", indicating that his peers might value his opinion.

Applicant argues that WO 02/053092 demonstrates that oral tolerance can be accomplished.

Applicant's interpretation of the reference is noted. A complete reading of the reference, however, shows that numerous difficulties have been encountered in attempts to induce oral tolerance, difficulties not addressed in the instant application.

Applicant argues "The Examiner has discounted the evidence presented in the references by Husby et al. (1994) and McKown et al. (2000) that were provided by Dr. Jevnikar, which demonstrate the induction of tolerance in humans." Applicant reviews the findings of Moldoveanu et al., 2004.

Applicant appears to misunderstand the Examiner's position, the evidence has not been "discounted"; it is the Examiner's position that a more complete examination of the author's work serves to demonstrate unpredictability as set forth above, particularly in view of the fact that the claims recite essentially no limitations regarding the types of immune responses to be suppressed. Interestingly, Applicant submits that Moldoveanu (2004) teaches that "oral tolerance may not decrease "pre-existing" responses when this pre-existing immune response to KLH is overly robust", an embodiment that would be encompassed by the instant claims.

Applicant reviews the findings of McKown et al. (1999) and Carbone et al. (2004). Applicant argues that their findings do not indicate unpredictability and comprise only routine experimentation. Applicant argues that the authors were not employing methods of trial and error.

It remains the Examiner's position that the references teach what they teach - a complete lack of efficacy. Regarding whether or not the authors were employing methods of trial and error, there would seem to be two possibilities, first, that they were indeed employing trial and error. Applicant has rejected this possibility. A second likely possibility then would be that the authors were employing methods that, given their expertise in the field, were judged most likely to prove successful. There is no evidence that the authors were attempting to fail. As the methods did, however, fail, said failure would seem to be a demonstration of the unpredictability of inducing immune tolerance in humans.

Applicant argues that the Examiner has "discounted" the testimony of Inventor Jevnikar.

Applicant is advised that the Inventor's declaration has not been "discounted", indeed, it was thoroughly evaluated as set forth previously.. However, in this instance the Inventor's opinion that his invention works has not been found to be persuasive, particularly in view of the evidence of record that it does not, for the reasons set forth here and previously.

Applicant argues "The Examiner's misapplication of the use of the term "unexpected" in Dr. Jevnikar's previous Declaration to support a basis of the rejection is an improper twisting of the inventor's meaning clearly contrary to what is true or was intended. It is inappropriate for the Examiner to remove the term "unexpected" from the context from which the term is used."

It is unclear how the Examiner has improperly twisted the term given that said term has not been used by the Examiner but rather was chosen by the Inventor, presumably in consultation with counsel.

Applicant argues "given the insight, guidance and examples provided by the disclosure of the present invention, the induction of tolerance in mammals in general and humans in particular is not so unpredictable as to render the claims of the application not enabled".

A review of the instant disclosure reveals that the eight examples deal exclusively with the production of the plants employed in the claimed method. It is unclear then how said examples could provide enablement for the claimed method. Looking to the rest of the disclosure for insight and guidance, the entire teaching of the disclosure comprises no more regarding dosages and timing of administration, i.e., parameters critical to the actual methods that would be used to induce the tolerance, than do the claims themselves. Thus, it is unclear where the insight and guidance referred to by Applicant is to be found.

Applicant argues that "The enablement requirement does not require that every variation of a method produce optimal results. Applicants have provided references describing that oral tolerance can be achieved in mammals".

The Examiner does not disagree. The Examiner has, however, provided numerous references showing that major embodiments of the claimed invention have failed and would be expected to continue to fail even now, some 12+ years past the priority date of the instant application. Accordingly, the invention as broadly claimed stands rejected as being unpredictable and requiring of undue experimentation.

Applicant's arguments, filed 10/09/07, have been fully considered but they are not persuasive. Applicant argues that the claimed methods include suppressing the immune response and encompass said suppression in animals.

Applicant's argument is noted. It is clear however, that the claimed method of suppression is assertedly accomplished by inducing tolerance and that the induction of tolerance in humans is a major embodiment of the claimed inventions. Note that the diseases disclosed at page 10 are seldom (if ever) treated in any animals except humans and human MHC is the only MHC

disclosed and discussed in the context of the claimed inventions.

Applicant submits Ergun-Longmire et al. (2004) in support of the claimed inventions.

First note that the reference was published some *eleven years* after the priority date of the instant application. Accordingly, it cannot show that the claimed inventions were enabled at the time of filing as is required. Regardless, the reference provides little if any support for the claimed inventions. Even after picking a very specific subset of patients, i.e., type 1 diabetic patients requiring insulin replacement for less than four weeks, the authors reported, "Disappointingly, there were no clinical benefits discernible from our oral insulin tolerance therapy as reflected in improved diabetes control, lowered glycated hemoglobin levels, or reduced daily insulin dosage," i.e., *the method did not work*.

Applicant sites the previously submitted declarations of the Inventor and references including Husby et al. (1994) and McKown et al (2000).

The Inventor's declarations and the references have been address previously as set forth above.

Applicant again discounts the teachings of the Marketletter (1999) reference.

As set forth in the reference, human clinical trials employing both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) were complete failures. Note that regarding Colloral the reference states that the trial did not achieve "statistical significance". Regarding Myloral, the reference states that Myloral "performed no better than placebo in Phase III trials".

Applicant again incorrectly argues that the Goodnow reference refers only to the action of corticosteroids.

As set forth above, the unpredictability of the reference also refers to methods of "chronically stimulating antigen receptors with antigen or antibodies to the receptor", i.e., methods of inducing tolerance".

Applicant cites WO 02/053092, page 22, lines 25-27 in support of the claimed inventions.

A reading of the entire paragraph shows that Applicant has misrepresented the reference's teachings. The paragraph makes clear some of the difficulties involved with attempts to establish immune tolerance. Interestingly, the paragraph from which lines 25-27 of page 22 are taken out of context also teaches, "Indeed, many studies have demonstrated the complexities inherent in manipulating the "balance between reacting and nonreacting" in the immune system. Zivny, et al (Clin Immunol 2001;101:150-68) clearly state that "*In* general, the response to one (tolerance inducing) antigen could not necessarily predict the response to another". Likewise, Hannihen et al (Diabetes 2001;50:771-75) observed that oral, nasal and respiratory administration of antigens caused appearance of disease symptoms (diabetes), rather than inducing tolerance". Clearly, this cite does *not* support Applicant's arguments for enablement.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 52, 59-61, 63, 69-91, and 95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07581 (1992, IDS) in view of U.S. Patent No. 5,484,719 (IDS).

As set forth previously, WO 92/07581 teaches a method (and product) for the induction of tolerance to MHC Class II proteins through the oral administration of an effective immunosuppressive dose of said proteins as a method for suppressing the rejection of engrafted donor tissues in humans (see particularly Summary of Invention, pages 7-8 and Class II MHC molecules pages 11-12).

The reference teaching differs from the claimed invention only in that it does not teach the use of a transgenic plant as the source of the oral tolerizing antigen.

The '719 patent teaches that transgenic plants comprise an inexpensive and convenient source of edible oral vaccines (antigens) (see particularly column 4,

lines 7-21). The reference further teaches a DNA construct for transforming a plant comprising a Cauliflower Mosaic Virus 35S promoter (see particularly column 8, lines 41-45) and nopaline synthase termination sequence (see particularly column 9, lines 29-30), and that said vaccines comprise partially purified extracts of leaves, stems, and seeds (see particularly column 6, line 60) of a potato or a tomato (see particularly column 7, lines 10-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method(and produce a product) for the induction of tolerance to MHC Class II proteins through the oral administration of an effective immunosuppressive dose of said proteins as a method for suppressing the rejection of engrafted donor tissues in humans, as taught by WO 92/07581. One of ordinary skill in the art at the time the invention was made would have been motivated to produce the antigen for said tolerance induction in the transgenic plant of the '719 patent comprising a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus 35S promoter and a nopaline synthase termination sequence, said antigen further comprising a partially purified extract of leaves, stems, and seeds of a potato or a tomato, because said transgenic plant would have provided an inexpensive and convenient source of said antigen, again as taught by the '719 patent. Note that the '719 patent teaches the administration of oral antigens for the induction of an immune response whereas the instant claims are drawn to the administration of oral antigens for the induction of tolerance. However, the induction of tolerance and the induction of an immune response can be considered two sides of the same coin. Indeed, some immunologists refer to the induction of tolerance as the induction of a suppressive immune response. Thus, the use of a transgenic plant as the source of an antigen for the induction of an immune response renders the use of a transgenic plant as the source of an antigen for the induction of tolerance obvious.

As set forth in the action of 4/08/05, The Inventor argues that the '719 patent is not relevant because it teaches expressing only harmful viral, bacterial, or fungal antigens in a plant.

It is the Examiner's position that sound scientific reasoning would lead the ordinarily skilled artisan to the conclusion that if viral, bacterial, and fungal antigens could be efficiently produced in a plant, so could tolerogenic antigens. As set forth previously, WO 92/07581 teaches that tolerance as the induction of a suppressive immune response. Accordingly, this combined knowledge renders the inventions of the instant claims, i.e., compositions and methods for the induction of a suppressive immune responsive comprising administering antigens produced in plants orally, obvious.

As set forth in the action of 1/11/06, Applicant's arguments, filed 10/18/05, have been fully considered but they are not persuasive. Applicant argues a lack of motivation to combine the references.

As set forth previously, it is the Examiner's position that sound scientific reasoning would lead the ordinarily skilled artisan to the conclusion that if viral, bacterial, and fungal antigens could be efficiently produced in a plant, so could tolerogenic antigens - there is no teaching of record that tolerogenic antigens differ from any other type of antigens. Antigens are routinely defined as substances capable of inducing an immune response. As set forth previously, WO 92/07581 teaches that tolerance as the induction of a suppressive immune response. Accordingly, this combined knowledge renders the inventions of the instant claims, i.e., compositions and methods for the induction

of a suppressive immune responsive comprising administering antigens produced in plants orally, obvious.

Applicant's arguments, filed 10/09/07, have been fully considered but they are not persuasive. Applicant argues that the references do not teach every element of the claimed invention but argues against the references individually.

Applicant is advised that it is the combined references in light of the knowledge generally available to one of ordinary skill in the art that renders the claimed inventions obvious.

Applicant again argues a lack of motivation to combine the references.

See the Examiner's remarks in the Office Action of 1/11/06 reiterated above. Again note that the primary reference, WO 92/07581, teaches how to administer antigens to achieve a tolerogenic effect.

Applicant argues that an award to the Inventor by the Kidney Foundation of Canada comprises a "secondary indica of non-obviousness". Applicant further asserts that the claimed inventions meet a long felt but unmet need.

The Inventor's award is noted. The press release submitted by Applicant does not address the specific inventions of the instant application. Regarding the long felt but unmet need, Applicant's one sentence assertion is not found to be persuasive.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 63, 69-71, 78-83, and 88-95 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 11-16 of U.S. Patent Application No. 10/137,647. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '647 application are drawn to the same product (an antigen for suppressing an immune response) of the instant claims. The addition of an immunosuppressive cytokine to the product of the claims of the '647 application does not render the claims patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has not addressed this rejection.

9. The following are new grounds of rejection necessitated by Applicant's filing of an additional application.

10. Claims 52, 59, and 60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 17-19, 34, and 53 of U.S. Patent Application No. 11/815,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '359 application are drawn to the same method of administering an antigen obtained from a transgenic plant as are the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. No claim is allowed.

12. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

14. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

12/28/07

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